Full-length HLA-G1 and truncated HLA-G3 differentially increase HLA-E surface localization.

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Public Summary:
Human leukocyte antigen (HLA)-E and -G belong to the non-classical major histocompatibility (MHC) class Ib family, widely recognized for its limited polymorphism. Although HLA-E mRNA has been widely detected in postnatal tissues, its surface expression is restricted due to the requirement that specific short peptides bind its α-chain to facilitate endoplasmic reticulum (ER) egress. Examples of such peptides include nonamers derived from N-terminal leader sequences of HLA class I proteins, all of which possess different binding affinities for HLA-E and variable effects on HLA-E surface localization. Evidence to date suggests HLA-A2 and HLA-B7 signal peptides possess the highest affinity for HLA-E with the greatest enhancement of surface expression. Recent studies found the peptide present in the leader sequences of the human cytomegalovirus glycoprotein UL40 could also enhance HLA-E surface expression. Although the direct tolerogenic role of HLA-G has been well established, its indirect tolerogenic effects through HLA-E remain unclear. One study demonstrated that the truncated and soluble isoforms of HLA-G are less efficient in providing HLA-E ligand to enhance ER egress. However, others believe that the truncated isoform, HLA-G3, is sufficient to upregulate HLA-E surface expression despite not reaching the cell surface itself. Thus, the effects of full-length versus truncated isoforms of HLA-G on HLA-E surface localization remain unclear. In this study, we clarify this question by assessing HLA-E surface expression in human cells heterologously expressing HLA-G1 and -G3. Our study revealed that HLA-E surface localization could be upregulated by not only full-length but also truncated HLA-G although the latter resulted in less efficient HLA-E translocation. This suggests that full-length and truncated isoforms may serve unique functional roles in immune regulation, and further underscores the importance of conducting additional studies aimed at clarifying the mechanisms underlying this differential regulation.

Scientific Abstract:
Human leukocyte antigen (HLA)-E plays a role in immune tolerance induction and its transport to the cell surface is limited and dependent on the availability of HLA class I signal peptide. The role of HLA-G in regulating HLA-E surface localization remains controversial. The aim of our study was to clarify whether full-length and truncated HLA-G isoforms regulate HLA-E surface localization. Using a retroviral expression system and flow cytometric analysis, we found that surface HLA-E levels were significantly higher in HLA-G1 (34.1+/-4.4%, $p<0.005$) and -G3 (15.3+/-1.8%, $p<0.04$) versus empty vector (9.0+/-1.0%) transductants. Biotinylation and Western blot studies revealed HLA-E surface protein was increased by 4.5- and 1.3-fold in HLA-G1 and -G3 versus empty vector transductants. Although no significant differences in transcript and protein levels were detected between HLA-G1 and -G3 transductants, surface levels of HLA-G1 were 2.5-fold higher than HLA-G3 by flow cytometric analysis and Western blotting. Taken together, our data demonstrate that full-length HLA-G1 and truncated -G3 differentially increase HLA-E surface localization.